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PERMUTATION TESTS FOR K-SAMPLE BINOMIAL DATA. (U)  
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MRC Technical Summary Report # 1701

## PERMUTATION TESTS FOR k-SAMPLE BINOMIAL DATA

Andrew P. Soms

**Mathematics Research Center  
University of Wisconsin—Madison  
610 Walnut Street  
Madison, Wisconsin 53706**

November 1976

(Received September 28, 1976)

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MATHEMATICS RESEARCH CENTER

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ABSTRACT

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The asymptotic distributions of the test statistics are derived and some numerical examples presented. Sample size guidelines are given for computer implementation of the tests.

AMS(MOS) Subject Classification - 62G10

Key Words - k-Sample Problem, Permutation Tests, Binary Data

Work Unit Number 4 - Probability, Statistics and Combinatorics

## Permutation Tests for k-Sample Binomial Data

Andrew P. Soms\*

### Summary

Exact k-sample permutation tests for binary data for three commonly encountered hypotheses are presented. The asymptotic distributions of the test statistics are derived and some numerical examples presented. Sample size guidelines are given for computer implementation of the tests.

### 1. Introduction

Let  $Y_{ij}$ ,  $1 \leq i \leq r$ ,  $1 \leq j \leq k_i$ , be independent Bernoulli random variables with parameters  $p_i$  and observed values  $y_{ij}$  and let  $m_1 = \sum_{i=1}^r \sum_{j=1}^{k_i} y_{ij}$ ,  $m_0 = \sum_{i=1}^r k_i - m_1$  and  $k = \sum_{i=1}^r k_i$ . The three hypotheses of interest are  $H_1: p_i = p_1$ ,  $2 \leq i \leq r$ , against the  $2^{r-1}-1$  alternatives that  $p_i > p_1$  if  $i \in A$  and  $p_i = p_1$  if  $i \in A^C$ , where  $A$  is any subset of  $\{2, \dots, r\}$ ,  $H_2: p_i = p_j$  for all  $i \neq j$  against the alternatives that a specified subset of pairs  $(i, j)$  are different, and  $H_3:$   $p_1 = p_2 = \dots = p_r$  against the alternative that  $\underline{p_1 \leq p_2 \leq \dots \leq p_r}$  with at least one strict inequality.

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\*Department of Mathematics, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201.

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Sponsored by the United States Army under Contract No. DAAG29-75-C-0024 and the University of Wisconsin-Milwaukee.

In the usual terminology,  $H_1$  corresponds to the one-sided comparison of  $r-1$  treatments to a control with upward shifts in the  $p_i$ 's being of interest,  $H_2$  to the one-way ANOVA for 0-1 data, and  $H_3$  to testing for the presence of a dose response (here it is assumed that the labelling index  $i$  corresponds to the  $i^{\text{th}}$  dose level).

First, consider  $H_1$ , the problem of comparing  $r-1$  treatments to a control with a one-sided alternative being of interest, similar comments applying to  $H_2$ . Some examples are: advertising effectiveness of  $r-1$  new methods against the existing or standard and drug side reactions of  $r-1$  new drugs against the standard. For  $r > 2$  there has been no exact treatment of this problem--some possibilities that have been given in the literature are the likelihood ratio, one-way normal ANOVA, or the Kruskal-Wallis test. In addition to being approximate (because of ties), these tests have another drawback--they merely test the null hypothesis of equality but give no further information in case of rejection, i.e., they do not tell which alternative to accept. If Scheffé type procedures are used for the ANOVA or Kruskal-Wallis, then even in the continuous case they are conservative--e.g., comparison of the S-intervals to the multivariate t intervals for the normal ANOVA shows the S-intervals to be longer. Here, of course, the additional problem of discrete data exists. Thus F-type

tests are not appropriate for this problem nor for H<sub>2</sub>. If unbiasedness for H<sub>1</sub> and H<sub>2</sub> is defined in a reasonable manner, it follows from the results of Lehmann [9] that no unbiased test exists, and hence consistency is the best one can hope for.

H<sub>3</sub> is the hypothesis of interest in quantal assay. It is also of interest in the toxicological testing of drugs where often the criterion of toxicity is whether a dose response exists. A common situation in drug testing is to have a control group and three dose groups--low, medium, and high--of randomly selected small test animals. After a period of administering the drug, the number of deaths, unfavorable reactions, or some other appropriate toxicity criterion is observed for its presence or absence in each animal and it is desired to test for dose response. In the continuous case such tests are known (see, e.g., [8], pp. 232-8), but here again the problem of ties exists. The simple permutation test proposed here is shown to be consistent.

The purpose of this paper is to present a unified approach to H<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub> based on permutation tests.

## 2. Permutation Tests for H<sub>1</sub> and H<sub>2</sub>

In all that follows the notation in 1. will be used.

Under H<sub>1</sub>, H<sub>2</sub>, or H<sub>3</sub>,  $Y = \sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}$  is a complete and

sufficient statistic (see, e.g., [3], p. 31 and p. 19) and hence any  $\alpha$ -level test also has conditional level  $\alpha$  and so it is sufficient to specify a conditional test.

The conditional distribution of  $Z_i = \sum_{j=1}^{k_i} Y_{ij}$ ,  $1 \leq i \leq r$ ,

given  $Y = m_1$  is

$$P[Z_i = n_i, \sum_{l=1}^r n_l = m_1, 1 \leq i \leq r] = \frac{\prod_{l=1}^r \binom{k_l}{n_l}}{\binom{m_0 + m_1}{m_1}} \quad (2.1)$$

and the carrier set is given recursively by

$$\begin{aligned} & \max(0, k_r - m_0) \leq n_r \leq \min(m_1, k_r) \\ & \cdot \\ & \max(0, \sum_{j=1}^r k_j - \sum_{j+1}^r n_j - m_0) \leq n_j \leq \min(m_1 - \sum_{j+1}^r n_j, k_j) \\ & \cdot \\ & \max(0, \sum_{i=1}^r k_i - \sum_{i=2}^r n_i - m_0) \leq n_1 \leq \min(m_1 - \sum_{i=2}^r n_i, k_1). \end{aligned} \quad (2.2)$$

These inequalities for  $n_j$  are obtained by requiring that the interval for  $n_{j+1}$  be nonempty, which is the case if and only if each of the two expressions on the right is greater than or equal to the two expressions on the left.

Elimination of redundancies yields the interval for  $n_j$ .

The interval for  $n_r$  is deduced directly from the constraints  $\sum_{l=1}^r n_l = m_1$  and  $\sum_{l=1}^r (k_l - n_l) = m_0$ . Note that if

$\tilde{y}_i = (y_{il}, \dots, y_{ik_i})$ ,  $\tilde{y} = (\tilde{y}_1, \dots, \tilde{y}_r)$  and if each permutation

of  $\tilde{y}$  has probability  $1/(m_0 + m_1)! = 1/k!$ , then the conditional distribution is (2.1). This important fact will allow the use of the Wald-Wolfowitz-Noether Theorem to obtain the limiting distribution of the test statistics. For the sake of completeness the statement is given here (see [3], p. 237 for the details). Let  $c_{1n}, \dots, c_{nn}$  and  $a_{1n}, \dots, a_{nn}$  be two sequences, each containing at least two distinct values, such that for all  $r = 3, 4, \dots$  the condition  $W$

$$\frac{\frac{1}{n} \sum_{i=1}^n (c_{in} - \bar{c}_n)^r}{[\frac{1}{n} \sum_{i=1}^n (c_{in} - \bar{c}_n)^2]^{r/2}} = O(1) \quad (2.3)$$

and for some  $r > 2$  the condition  $N$

$$\lim_{n \rightarrow \infty} \frac{\frac{1}{n} \sum_{i=1}^n |a_{in} - \bar{a}_n|^r}{[\frac{1}{n} \sum_{i=1}^n (a_{in} - \bar{a}_n)^2]^{r/2}} = 0 \quad (2.4)$$

is satisfied, where  $\bar{c}_n = \frac{1}{n} \sum_{i=1}^n c_{in}/n$  and  $\bar{a}_n = \frac{1}{n} \sum_{i=1}^n a_{in}/n$ .

Let  $\tilde{X}_n = (X_1, \dots, X_n)$  be a random variable

which takes on each permutation of  $(a_{1n}, \dots, a_{nn})$  with probability  $1/n!$  and let  $L_n = \sum_{i=1}^n c_{in} X_i$ . Then

$$E\{L_n\} = (\sum_{i=1}^n c_{in} \sum_{j=1}^n a_{jn})/n \text{ and}$$

$$\text{Var}\{L_n\} = \frac{1}{n-1} \sum_{i=1}^n (c_{in} - \bar{c}_n)^2 \sum_{j=1}^n (a_{jn} - \bar{a}_n)^2 = \sigma_{L_n}^2 \text{ and}$$

$(L_n - EL_n)/\sigma_{L_n}$  converges in distribution to the standardized normal.

Let  $Z = \max_{2 \leq i \leq r} \frac{\bar{Z}_i - \bar{Z}_1}{(1/k_i + 1/k_1)^{1/2}}$ , where  $\bar{Z}_i = Z_i/k_i$ ,

$1 \leq i \leq r$ . The descriptive level associated with the

$i^{\text{th}}$  group is  $P[Z \geq \frac{\bar{y}_i - \bar{y}_1}{(1/k_i + 1/k_1)^{1/2}}]$ , where  $\bar{y}_i = \sum_{j=1}^{k_i} y_{ij}/k_i$ ,

$i \leq i \leq r$  ( $P[\cdot]$  stands for (2.1)). For any choice of the  $r-1$  possible descriptive levels,  $H_1$  or one of the  $2^{r-1} - 1$  alternatives is accepted as follows: if the descriptive level associated with the  $j^{\text{th}}$  group is less than or equal to the chosen descriptive level, the  $j^{\text{th}}$  group belongs to the set different from the control, otherwise it is in the set equal to the control. This type of simultaneous permutation test has been suggested in Miller ([10], p. 180) for continuous data and equal sample sizes. Generally, except for small  $m_1$  or  $m_0$ , the test has to be carried out on a computer and (2.2) is very convenient for a nested do-loop procedure, each point in the carrier set being tested  $r-1$  times and the probabilities summed in the innermost do-loop. The number of cases in the carrier set for four groups of equal sample size as a function of the group size is given in the table.

1. Number of Cases for Four Groups of Equal Size with Half Ones

<u>Group size</u>	<u>Number of cases</u>
5	146
10	891
20	6 181
30	19 871
40	45 961
80	354 321
100	686 901

Consider now the asymptotic behavior of the permutation test under the assumption that  $\lim_{k_i \rightarrow \infty} k_1/k_i = c_i > 0$ ,  $2 \leq i \leq r$ .

$$\text{Let } L_i = \frac{\bar{Z}_i - \bar{Z}_1}{(1/k_i + 1/k_1)^{1/2} \left( \sum_{i=1}^r \sum_{j=1}^{k_i} (y_{ij} - \bar{y})^2 / (k-1) \right)^{1/2}}, \quad 2 \leq i \leq r,$$

$\bar{y} = \sum_{i=1}^r \sum_{j=1}^{k_i} y_{ij} / k$ . It follows that  $E\{L_i\} = 0$ ,  $\text{Var}\{L_i\} = 1$ ,

$$\text{Corr}(L_i, L_j) = (k_i k_j / ((k_1 + k_i)(k_1 + k_j)))^{1/2}, \quad i \neq j \quad ([3], \text{ p. 240}).$$

By a slight extension of the argument given on pp. 244-5 of [3] it follows that under H1, H2, H3 or the three alternatives (more generally, simply under the assumption that there are  $r$  groups with  $p_i$  the parameter for the  $i^{\text{th}}$  group) (2.4) is satisfied with probability one for  $r = 3$ . Also, it is seen

by direct verification that (2.3) holds for the coefficients of each permutation statistic  $\bar{Z}_i - \bar{Z}_1$ ,  $2 \leq i \leq r$ , so each  $L_i$  is marginally normal. By considering arbitrary linear combinations of the scaled ([3], p. 241)  $\bar{Z}_i - \bar{Z}_1$ ,  $2 \leq i \leq r$ , it follows by the Wald-Wolfowitz-Noether Theorem that the limiting joint distribution of  $L_2, \dots, L_r$  is asymptotically normal with mean 0 and variance-covariance matrix  $R = [\rho_{ij}]$ ,  $\rho_{ij} = 1/(1+c_i)(1+c_j)^{1/2}$  if  $i \neq j$ ,  $\rho_{ij} = 1$  if  $i = j$  (it is checked directly that (2.3) is satisfied). Since the  $L_i$ ,  $2 \leq i \leq r$ , differ only by a scaling factor from the  $(\bar{Z}_i - \bar{Z}_1)/(1/k_i + 1/k_1)^{1/2}$ , the permutation test may be equivalently performed with the  $L_i$ 's. So an approximation to the descriptive level associated with the  $i^{\text{th}}$  group is

$$P \left[ \max_{2 \leq j \leq r} X_j \geq \frac{\bar{y}_i - \bar{y}_1 - 1/(2\bar{k}_i)}{(1/k_i + 1/k_1)^{1/2} \left( \sum_{i=1}^r \sum_{j=1}^{k_i} (y_{ij} - \bar{y})^2 / (k-1) \right)^{1/2}} \right] =$$

$$1 - P \left[ X_j \leq \frac{\bar{y}_i - \bar{y}_1 - 1/(2\bar{k}_i)}{(1/k_i + 1/k_1)^{1/2} \left( \sum_{i=1}^r \sum_{j=1}^{k_i} (y_{ij} - \bar{y})^2 / (k-1) \right)^{1/2}}, 2 \leq j \leq r \right],$$

where  $\bar{k}_i = (k_i + k_1)/2$ , the  $X_i$  are multivariate normal with means 0 and variance-covariance matrix  $R$  (here it is assumed that  $c_i = k_1/k_i$ ), and a continuity correction has been used. This probability may be obtained by linear interpolation in the table of Gupta [4] for the case of equal  $k_i$ 's (for the case

of unequal  $k_i$ 's a procedure is given below). As an example, for four groups of forty each, with half ones, such that

$\max_{2 \leq j \leq 4} (Z_j - Z_1) = 10$ , the exact probability associated with

this value is .043, while the approximation from Gupta's tables (using 2.12 as the value) gives .044.

The above results will now be used to give a brief discussion of consistency. Assume that randomized tests are used to achieve a significance level  $\alpha$  and that  $t_\alpha(Z)$  is the randomized cut-off point for the  $L_i$ 's. By the above,  $t_\alpha(Z)$  converges almost surely to  $d_\alpha$ , where

$P[X_i \leq d_\alpha, 2 \leq i \leq r] = 1 - \alpha$ . Hence the limiting form of the permutation test is to say  $p_i = p_1$  if

$$\frac{\bar{y}_i - \bar{y}_1}{\sqrt{(1/k_i + 1/k_1)^{1/2} (\sum_{i=1}^r \sum_{j=1}^{k_i} (y_{ij} - \bar{y})^2 / (k-1))^{1/2}}} < d_\alpha \text{ and if not,}$$

to conclude  $p_i > p_1$ .

$$\text{Let } T_i(Y) = \frac{\bar{Y}_i - \bar{Y}_1}{\sqrt{(1/k_i + 1/k_1)^{1/2} (\sum_{i=1}^r \sum_{j=1}^{k_i} (Y_{ij} - \bar{Y})^2 / (k-1))^{1/2}}},$$

$$2 \leq i \leq r, \quad \bar{Y}_i = \sum_{j=1}^{k_i} Y_{ij} / k_i, \quad \bar{Y} = \sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij} / k, \quad Y = (Y_{11}, Y_{12}, \dots, Y_{r, k_r}),$$

i.e., the  $T_i$ 's are the unconditional permutation statistics. By considering linear combinations, it is seen that the limiting

$$\text{joint distribution of } \frac{\bar{Y}_i - \bar{Y}_1 - (p_i - p_1)}{d_i^{k_i} (\sum_{i=1}^r \sum_{j=1}^{k_i} (Y_{ij} - \bar{Y})^2 / (k-1))^{1/2}},$$

$2 \leq i \leq r$ , is the multivariate normal with 0 means and unit variances and correlations that are functions of  $c_i$ ,  $2 \leq i \leq r$ , and  $p_i$ ,  $1 \leq i \leq r$ , where the

$d_i = ((c_i p_i q_i + p_1 q_1) / (c_i + 1))^{1/2}$  are positive constants

with  $c$  the almost sure limit of  $(\sum_{i=1}^r \sum_{j=1}^{k_i} (Y_{ij} - \bar{Y})^2 / (k-1))^{1/2}$

and  $q_i = 1 - p_i$ ,  $1 \leq i \leq r$ . Then, by the same argument as in Hoeffding ([6] p. 171), the limiting probability of any one of the  $2^{r-1}$  decisions is (here  $(X_2, \dots, X_r)$  has the limiting distribution)

$$\lim_{k_i \rightarrow \infty, 1 \leq i \leq r} P[X_i \geq \frac{d_\alpha}{d_i} - \frac{p_i - p_1}{d_i^{1/2}}] = \frac{p_i - p_1}{d_i^{1/2}}, \quad 2 \leq i \leq r,$$

where the  $d'_i = ((c_i p_i q_i + p_1 q_1) / (c_i + 1))^{1/2}$  are positive constants. So if  $p_2 > p_1, \dots, p_{r_1} > p_1$ , then with limiting probability 1 they will be identified as being bigger than  $p_1$ . The limiting probability of correct decision is  $P[X_{r_1+1} \leq d_\alpha/d_{r_1+1}, \dots, X_r \leq d_\alpha/d_r]$ .

The procedure and results for the two-sided case and the one-way ANOVA are very similar. For the two-sided case of treatment to control comparisons absolute values are used in the definition of  $Z$  and for the constants for which

the descriptive levels are to be found. The approximations to the descriptive values, for the case of equal treatment group sizes, can be found, just as before, by linear interpolation in the tables of Dunn, Kronmal, and Yee [1]. For unequal treatment group sizes the interpolating scheme given in Dutt, Mattes, Soms, and Tao [2] can be used for both the tables in [1] and [4]. Briefly, the procedure consists of calculating an effective treatment group size  $\bar{k} = \sum_{i=2}^r k_i / (r-1)$  and using  $\bar{k}$  as the equal treatment group size to obtain an approximation as discussed above. The comparisons in [2] of the approximation to the exact values indicate that the approximation is adequate for all practical purposes.

For all comparisons, consider

$$Z = \max_{i,j} \frac{|\bar{z}_i - \bar{z}_j|}{(1/k_i + 1/k_j)^{1/2}}, \quad i \neq j,$$

and compare this to the corresponding observed quantities. The approximation to the exact descriptive level (after division by the sum of squares as before) can be found in the tables of Harter [5] for the case of equal group sizes. In the case of unequal group sizes, dropping the continuity correction, interpolation can be used on the degrees of freedom, as discussed by Keselman, Toothaker, and Shooter [7], where one of the methods mentioned is to use the harmonic mean of the sample sizes to obtain an effective equal sample

size. Note that the tabulated values in [5] must be divided by  $\sqrt{2}$ . As an example, for four groups each of size 40 with 15, 18, 20, and 27 ones, the exact probability is

$P[\max_{i < j} |Z_i - Z_j| \geq 12] = .049$ , while the approximation from

[5] (using 2.56 as the value) is .051.

Numerical examples of H1 and H2 are now given. Suppose that three new advertising techniques are to be compared to the existing, each method given to 20 of 80 randomly chosen people and the response is "like - 1" or "dislike - 0". Control gets 6 ones, the first method 14, the second 13, and the third 7. Carrying out the exact test, it is found that for  $\alpha = .051$ , the first and second methods are better than the control. For the one-way ANOVA, suppose there are four different therapies for a disease, with each either having or not having a side effect on a subject. It is desired to test whether all are the same with respect to incidence of side reactions. The experimental set-up is as above, with 1 standing for the absence and 0 for the presence of a side reaction. Therapy 1 gets 6 ones, 2 gets 8 ones, 3 gets 15 ones, and 4 gets 11 ones. Then at the .035 level it is concluded that 3 and 1 are different.

### 3. A Permutation Test for Dose Response

A reasonable parameter to measure the extent of dose response is  $\Delta = \sum_{i>j} (p_i - p_j) = \sum_{i=2}^r \sum_{j=1}^{i-1} (p_i - p_j) = \sum_{i=1}^r (2i-r-1)p_i$ ,

which is just a linear combination of the  $p_i$ 's, the largest indexes receiving the largest weights. Therefore the permutation test here proposed is to reject  $H_0$  for large values of  $L = \sum_{i=1}^r (2i-r-1)Z_i/k_i$ , given  $Z = \sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}$ . As

before,  $E\{L\} = 0$  and  $Var\{L\} = \sigma_L^2 = \frac{1}{k-1} \sum_{i=1}^r \frac{(2i-r-1)^2}{k_i} \sum_{i=1}^r \sum_{j=1}^{k_i} (y_{ij} - \bar{y})^2 = \frac{1}{k-1} m_1 \left(1 - \frac{m_1}{k}\right) \sum_{i=1}^r \frac{(2i-r-1)^2}{k_i}$ . Hence by the Wald-Wolfowitz-

Wolfowitz-Noether Theorem,  $L/\sigma_L$  converges in distribution to the standardized normal and this can be used as the asymptotic version of the test (It is verified directly that (2.3) is satisfied). For four groups with equal sample size

$s, \sigma_L^2 = \frac{20 m_1 (1-m_1/4s)}{s(4s-1)}$ , which reduces to  $20/(4s-1)$  when  $m_1 = 2s$ . As an example, suppose in a toxicity test 40 animals are put on each of control, low, medium, and high doses and at the end of the test there are 16, 20, 20, and 24 deaths, respectively. Then the exact probability is  $P[L/\sigma_L \geq 1.69] = .052$ , while the limiting normal value with continuity correction is .049, corresponding to 1.66.

An approximation that works even better is to use the

continuity correction and regard  $(L-1/2\bar{k})/\sigma_L$  as a t with  $\frac{4}{k}$  degrees of freedom, where  $\bar{k} = \sum_1^r k_i/4$ . For the above this gives .053 as the approximation. Consider now the question of consistency. From above,  $L/\sigma_L$  converges in distribution to the standard normal and it is known that the same is true for the unconditional random variable

$$\frac{\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}/k_i - \Delta}{(\sum_{i=1}^r (2i-r-1)^2 \frac{p_i q_i}{k_i})^{1/2}} \text{ and hence the limiting distribution of}$$

$\frac{\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}/k_i - \Delta}{\sigma_L (\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij})}$  is normal with 0 mean and positive variance  $\sigma^2$ , where  $\sigma_L^2(\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij})$  is  $\sigma_L^2$  with  $m_1$  replaced by  $\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}$ . Therefore the limiting probability of rejection

$$\text{is } \lim_{\frac{k_1}{k_i} \rightarrow c_i, 2 \leq i \leq r} P \left[ \frac{\sum_{i=1}^r \sum_{j=1}^{k_i} Y_{ij}/k_i - \Delta}{c(1/k)^{1/2}} \geq \frac{z_\alpha}{c'} - \frac{\Delta}{c(1/k)^{1/2}} \right],$$

where  $z_\alpha$  is the standardized normal upper  $100\alpha^{\text{th}}$  percentile and  $c$  and  $c'$  are positive constants, and therefore the test is consistent for positive  $\Delta$ .

For  $r = 2$  the test given here reduces to Fisher's exact test.

#### 4. Concluding Remarks

The tests here described are suitable for computer implementation. For the case of equal sample sizes and an equal split of 0's and 1's the approximate limitations on each group size are 100 for  $r = 4$ , 40 for  $r = 5$ , 20 for  $r = 6$  and 10 for  $r = 7$ . For the case of less or more ones these limits increase, because it is to be expected that the carrier set is largest for an equal split of 0's and 1's. Fortunately, for the case of toxicological testing often  $r = 4$ , and hence it should almost always be possible to carry out the exact test. For  $r \geq 8$ , hopefully power considerations would lead to sample sizes for which the asymptotic versions of the permutation tests could be used whenever  $m_1$  or  $m_0$  are moderate, the exact tests being run only for small  $m_1$  or  $m_0$ .

Listings of short computer programs that carry out the tests for  $H_1$ ,  $H_2$ , and  $H_3$  are available on request from the author. These programs were used for the examples discussed above.

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## UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 1701	2. GOVT ACCESSION NO. <i>(9)</i>	3. RECIPIENT'S CATALOG NUMBER <i>Technical</i>
4. TITLE (and Subtitle) PERMUTATION TESTS FOR k-SAMPLE BINOMIAL DATA		5. TYPE OF REPORT & PERIOD COVERED Summary Report, no specific reporting period
6. AUTHOR(s) <i>(10) Andrew P. Soms</i>	7. CONTRACT OR GRANT NUMBER(s) <i>(15) DAAG29-75-C-0024</i>	8. PERFORMING ORGANIZATION NAME AND ADDRESS Mathematics Research Center, University of Wisconsin 610 Walnut Street Madison, Wisconsin 53706
9. PERFORMING ORGANIZATION NAME AND ADDRESS See Item 18 below.	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS <i>(11)</i>	11. REPORT DATE <i>November 1976</i>
12. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) <i>(14) MRC-PSR-1701</i>	13. NUMBER OF PAGES <i>17</i>	14. SECURITY CLASS. (of this report) UNCLASSIFIED
15. DECLASSIFICATION/DOWNGRADING SCHEDULE <i>(12) 18p.</i>		
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES U. S. Army Research Office P. O. Box 12211 Research Triangle Park North Carolina 27709      University of Wisconsin-Milwaukee Milwaukee, Wisconsin 53201		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) k-Sample Problem, Permutation Tests, Binary data		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Exact k-sample permutation tests for binary data for three commonly encountered hypotheses are presented. The asymptotic distributions of the test statistics are derived and some numerical examples presented. Sample size guidelines are given for computer implementation of the tests.		